EXHIBIT 3

(Redacted)

(Unredacted Version To Be Filed Under Seal)

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO
EASTERN DIVISION

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KEVIN D. HARDWICK,

Plaintiff,

v.

3M COMPANY; E. I. DU PONT DE NEMOURS AND COMPANY; THE CHEMOURS COMPANY LLC; ARCHROMA MANAGEMENT LLC; ARKEMA, INC.; ARKEMA FRANCE, S.A.; AGC CHEMICALS AMERICAS, INC.; DAIKIN INDUSTRIES LTD.; DAIKIN AMERICA, INC.; SOLVAY SPECIALTY POLYMERS, USA, LLC,

Defendants.
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Case No. 2:18-cv-01185

Judge Edmund A. Sargus, Jr.

Chief Magistrate Judge Elizabeth A. Preston Deavers
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EXPERT REPORT OF JESSICA HERZSTEIN, M.D., M.P.H.
December 14, 2020

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Summary of Opinions

At the request of 3M Company, E. I. du Pont de Nemours and Company, The Chemours Company, Archroma Management LLC, Arkema, Inc., Arkema France, S.A., AGC Chemicals Americas, Inc., Daikin Industries Ltd., Daikin America, Inc., and Solvay Special Polymers, USA, LLC, I reviewed and evaluated materials related to plaintiff's motion for certification of the proposed nationwide class of "any individual residing within the United States at the time of class certification for one year or more since 1977 with at least 0.05 parts per trillion (ppt) of PFOA and at least 0.05 ppt or more of any other PFAS chemical in their blood serum" for whom plaintiff purports to seek class-wide medical monitoring. A high-level summary of my opinions following that review appears below.

1. While medical screening or medical monitoring can sometimes be beneficial for certain diseases in certain individuals, medical screening is often unnecessary, unhelpful, or dangerous depending on the individual.[1]

2. In order to benefit those individuals who undergo testing, and to reduce the risk of unnecessary and harmful testing among healthy persons, medical science dictates that each screening test be evaluated individually with reference to a specific disease in a specific population in which the disease has been studied from an epidemiological perspective. When testing is considered for persons where exposures may cause specific latent disease, understanding the exposure-disease relationship is critical for determining who will benefit.

3. The core criteria for assessing the appropriateness of screening, including whether the benefits of testing outweigh the harms, are discussed in resources from the National Cancer Institute (NCI, Cancer Screening Overview PDQ), the United States Preventive Services Taskforce (USPSTF, Methods and Processes), the American Cancer Society (Smith 2017), the World Health Organization (Wilson and Jungner 1968), and the Agency for Toxic Substances and Disease Registry (ATSDR 1995):

    a. Screening must target a specific disease.

    b. The hazardous exposure must be known to cause the specific disease.

    c. The individual to be screened must be at significantly increased risk of a serious disease as a result of the exposure and must have no symptoms related to that disease.

    d. Screening tests for the disease must be reliable and accurate, and the prevalence of the disease must be high enough to justify screening for new cases.

    e. The benefits of the full screening and resulting evaluation must outweigh the risks.

[1] The terms "medical monitoring" and "medical screening" are used interchangeably in this report.

f. The clinical outcome must be improved as a result of the screening.

4. Medical screening will be unnecessary where the disease is already screened for as part of an individual's typical medical care regimen through their own personal physicians.

5. Medical screening will be unhelpful for individuals where there is no medical advantage to the early detection of the disease.

6. Medical screening will be harmful to individuals depending on their medical background, age, mental condition, and the type of diseases at issue.

7. Applying well-established screening standards, whether medical screening may be warranted for a specific individual will depend on a number of factors, such as:

   a. The scope and nature of the medical screening regimen;

   b. The disease in issue and the ability to reliably and accurately detect the disease;

   c. The disease in issue and the relative advantages of early detection;

   d. The individual's risk for developing the disease as a result of the exposure, which, assuming any elevated risk exists, would be a function of the exposure in terms of time (frequency and duration) and level of exposure and the individual's unique medical history and other characteristics;

   e. The individual's medical history, alternate exposures, lifestyle, other risks factors, and current state of health; and

   f. The informed consent and wishes of the individual.

8. Any medical screening regimen must include highly individualized follow-up and monitoring, which can cascade into a myriad of potential medical options, depending on the results of the initial screening and the variables outlined above, among others.

9. Because of the importance of numerous individual factors when it comes to assessing risk from exposure, background risk for specific diseases, and the risk-benefit balance from specific monitoring tests, whether and what sort of medical monitoring is appropriate cannot be determined on a class-wide basis. In other words, individual-specific considerations are critical to the determination of what medical monitoring, if any, is warranted in this case, and not just to the implementation of any such medical monitoring.

10. In this case, the plaintiff's assertion[2] that medical screening would be appropriate for the entire proposed class fails to account for any of these variables or to apply well-established screening standards:

   a. The plaintiff fails to identify what the proposed medical monitoring program actually consists of with any particularity, or to explain how any aspect of that program satisfies the basic standards for medical monitoring.

   b. If what plaintiff is proposing is a research study to evaluate the health risks, if any, of exposure, that would not be characterized as medical monitoring. By any means, what the plaintiff describes as "medical monitoring" would not be considered medical monitoring by the medical community.

   c. Rather than explain why he believes particular individuals are at an increased risk of a particular disease due to their exposure to a combination of PFOA and one of the other thousands of PFAS chemicals, the plaintiff simply assumes that all proposed class members are at increased risk of disease generally. He asserts that having at least 0.05 parts per trillion (ppt) or more of PFOA and 0.05 ppt of any other PFAS chemical in their blood puts every class member at risk of disease and at such a high risk of disease that they merit undergoing an array of testing for early detection of disease. This threshold level of exposure is not supported by science and, if accepted, would mean that essentially the entire population of the United States should receive special testing for supposed PFAS-exposure related conditions. Population-based medical monitoring requires identification of a specific population that, by virtue of its exposure, is at significantly increased risk for specific diseases as compared to the general population. If the proposed population for monitoring is the general population—as is proposed here—then, by definition, it is not at significantly increased risk compared to the general population, and special monitoring is not warranted.

   d. Whether any individual is at a significantly increased risk of disease due to exposure depends on the individual's relative exposure to PFAS and numerous individual characteristics, even assuming that any elevated risk exists at all.

   e. Many diseases are not easily or reliably detected, and for many of the conditions, there are no treatment advantages to early detection.

   f. The USPSTF has developed evidence-based guidelines for screening a subgroup or individual at high risk for a specific disease such as diabetes, colon cancer and hepatitis C. Many of these are common diseases, and the appropriateness of using the proven screening tests for these diseases in identified persons at high risk

[2] Though Plaintiff's Motion for Class Certification and the First Amended Class Action Complaint both request medical monitoring for the entire proposed class, plaintiff stated in his deposition that, rather than additional medical testing, he was instead interested in knowledge that might be gained from additional research into the potential health effects of PFAS exposure. (Hardwick Dep. Tr. at 133-134) When I refer to plaintiff's request for medical monitoring in this report, I am referring to the request made in the pleadings, notwithstanding plaintiff's testimony to the contrary.

depend on age and other individual-specific criteria. When individuals have had cholesterol testing or a specific cancer screening following USPSTF guidelines, there is no rationale and no benefit if the testing is repeated (e.g., due to environmental exposure risk) sooner than the recommended interval.

g. For many individuals, medical screening can be harmful. The harms of medical screening depend on various individual-specific factors, and cannot be fully evaluated on a class-wide basis.

h. It is important to use scientific methodology to identify specific individuals at high enough risk of a specific PFAS-related disease to offset the myriad adverse impacts of screening and testing. The plaintiff has not described any medical monitoring program, much less one that takes into account an individual's needs and the potential risks and benefits for each individual plaintiff. The named plaintiff is not representative of the proposed class in terms of their exposures, medical histories, lifestyles, and other unique characteristics, which demonstrates the need for individualized assessment to determine whether screening is warranted.

i. Medical screening decisions are best when left to the individual in consultation with his or her own physician based on each individual patient's own medical history, risks, and preferences. Persons in a community are more likely to see a benefit to and participate in screening when it is individually tailored and explained and initiated by their personal physician.

Background and Qualifications

I am a physician with over thirty years of training and experience in the fields of environmental and occupational medicine. I have been on the faculty at two universities in internal medicine, preventive medicine, public health and occupational medicine. I led the medical department in a multinational company, where I was responsible for workplace health. Currently, I am the President of Environmental Health Resources, P.C., a consulting company that focuses on developing occupational and environmental medical programs, including programs for health crisis management, medical screening, and risk assessment and risk communication. I have been involved in the design, evaluation, and implementation of medical monitoring programs for non-profit organizations and government agencies.

I graduated from Harvard College with an A.B. in Chemistry; from Yale University School of Medicine with a Medical Degree; and from Yale University School of Medicine with a master's degree in Public Health and Environmental Health.

I completed a residency in internal medicine and then a fellowship in occupational and environmental medicine and toxicology. I am a Fellow of the American College of Physicians and a Fellow of the American College of Occupational and Environmental Medicine. I served on the Agency for Toxic Substances and Disease Registry (ATSDR) expert panel that developed the Final Criteria for Determining the Appropriateness of a Medical Monitoring Program under CERCLA.

In 2012, I was appointed by the Secretary of Health and Human Services (HHS) to the United States Preventive Services Task Force (USPSTF), an independent, volunteer 16-member panel of primary care and preventive medicine experts who develop evidence-based standards for medical screening for the general population. The USPSTF was established by Congress in 1984. Its recommendations, which are developed through the application of procedures designed to guide its decision-making, cover specific, important clinical topics dealing with complex issues in the areas of medical screening, preventive counseling, and preventive medicine. The USPSTF guidance is widely followed by medical professionals in all specialties, and it sets the standard for reimbursement for preventive services, including screenings, by public and private insurers.

I served a full five-year term on the USPSTF during which time we evaluated evidence, analyzed risks and benefits, developed recommendations, and broadly disseminated educational materials for dozens of preventive services. Topics ranged from screening for hepatitis C, prostate cancer, diabetes, BRCA gene mutations, and thyroid disease to counseling for prevention of alcohol abuse.

I served as chair of the USPSTF Committee on Methods and the Committee on Dissemination and Implementation, and I served as the Task Force lead for a number of medical screening topics during the entire process of work plan development, data analysis, epidemiologic review, public response, and peer review and writing the recommendation standard. Publications related to my work on the USPSTF are listed on my curriculum vitae **(Exhibit A).**

From 1997 to 2014, I was the Global Medical Director for Air Products and Chemicals (Air Products), a multinational manufacturing company with over 20,000 employees. As Global Medical Director, I managed Air Products' worker health programs, medical surveillance, international travel health, health hazard assessment, health crisis preparedness and response, wellness, and mental health in more than 40 countries.

I have evaluated and provided care for workers who handle hazardous chemicals at work and/or at home. I have evaluated and advised community residents with concerns about toxic exposures relating to a wide spectrum of health hazards. I have presented at community meetings to address community health exposure concerns and have also taught hospital staff physicians and academic staff physicians about environmental health exposure and disease topics.

I teach occupational medicine residents each year at the University of Pennsylvania School of Medicine, Department of Occupational and Environmental Health. Throughout my career, I have held academic appointments at Harvard University, Temple University School of Medicine, the Medical College of Pennsylvania, and Northwestern University School of Medicine. I have taught medical students and health professionals on a wide variety of public health and occupational and environmental health topics.

I have also served as Medical Director for the United States Department of Defense, Defense Contract Management East, where I was responsible for the oversight of national medical programs, including medical screening. I was a consultant to the Harvard Institute of International Development and the United States Agency for International Development, working to develop a comprehensive environmental health program to address widespread contamination and community exposure to hazardous substances in Slovakia.

I have published articles on various topics in occupational and environmental health and general preventive health and medical screening. I am the lead author of *Environmental Medicine,* a textbook on environmental health, and have contributed chapters to books on occupational health and toxicology.

A copy of my curriculum vitae, which includes a list of my publications over the last ten years, appears at **Exhibit A.**

I am being compensated for my time at a rate of $550 per hour. Over the last four years, I have provided deposition testimony in *Strong v. Republic Services, Inc.,* St. Louis County Circuit Court (2019) and in *Baker v. Saint-Gobain Performance Chemicals*, U.S. District Court for the Northern District of New York (2020).

Materials Considered

In connection with the preparation of this report, I reviewed the materials listed below and the literature listed in **Exhibit B.** I am also familiar generally with other medical and scientific literature regarding medical monitoring and PFAS as it relates to human health.

1. The First and Amended Class Action Complaints in Hardwick v. 3M Co., United States District Court, Southern District of Ohio.

2. Plaintiffs' Motion for Class Certification dated 7/31/20.

3. The named plaintiff's medical records in this case.

4. The transcript of the named plaintiff's deposition in this case.

5. Blood test results for the named plaintiff.

6. Other materials that may not be identified in the above lists but are otherwise identified in this report.

Background Principles of Medical Monitoring

Decision-making about medical monitoring requires identifying those who are at a significantly increased risk of a specific disease and who will likely benefit from screening, and selecting screening tests that are likely to offer important benefits to the health of the person to be monitored. In order for screening to be warranted, the benefits must outweigh the potential adverse impacts of the testing and follow-up procedures. As discussed below, guidelines developed by scientific organizations provide a well-accepted structure for making these decisions. Key terms related to medical screening that will be used throughout this section are defined in **Table 1.**

Table 1. Medical Screening Terminology.

- **False positive —** A false positive test means that an individual without the disease is misclassified as having the disease on the basis of the screening test.
- **False negative —** A false negative test means that a person with the disease is misclassified as not having the disease on the basis of the screening test.
- **Prevalence —** The prevalence of disease is the proportion of persons in a specific population who have the disease.
- **Sensitivity —** Sensitivity refers to the proportion of persons with the target disease for whom a test correctly provides a positive test result.
- **Specificity —** Specificity refers to the proportion of persons without the target disease for whom a test correctly provides a negative test result. Other things being equal, tests with high specificity (low false positive rate) tend to have a high positive predictive value.
- **Positive predictive value —** The positive predictive value is the probability that an individual with a positive or abnormal test result actually has the disease. A good screening test has a high positive predictive value. The positive predictive value is a function of the prevalence and so must be defined for a specific disease in a specific population. Even if a test has a high sensitivity and specificity, its positive predictive value will be low if the prevalence of the target disease is low.
- **Negative predictive value —** The negative predictive value is the probability that an individual with a negative test result does not actually have the disease.

1. The Purpose of Medical Monitoring

- When physicians plan medical monitoring, they do so to screen for a specific disease or diseases for which the individual is at high risk, at a time when the person has no symptoms of the disease. For individuals exposed to a hazardous substance known to cause a latent disease, the persons to be screened must be at a significantly increased risk of that disease as a result of exposure in order for the program to offer a health benefit. The goal of medical monitoring is to use specific evidence-based screening tests as the first step in looking for a specific disease in someone at high risk for that disease (ATSDR). The goal is to improve a person's future health by finding and treating the specific disease earlier than would otherwise happen without screening tests. For this reason, screening is only appropriate where, among other things, early detection through screening is known to have a significant impact on the natural history of that disease.

- What the plaintiff describes as "medical monitoring" would not be considered medical monitoring by the medical community. Screening involves testing asymptomatic persons for early disease. What the plaintiff really seems to be proposing is a research study in which data will be collected and reviewed to learn about the health of the proposed class and to study the health effects, if any, associated with exposure. Medical monitoring is appropriate only when the specific health effects associated with a hazardous chemical and the dose-response relationship are known. (ATSDR)

- The purpose of screening is to benefit an individual who has no symptoms or signs of the disease, and who may well never have the disease. "Screening tests sort out apparently well persons who probably have a disease from those who probably do not." (ATSDR 1995) Since a screening test is not designed to be diagnostic, further testing and evaluation is needed for persons with positive/abnormal test results. This often initiates a cascade of testing. It is imperative to only do the screening and cascade of testing if there is a low and acceptable risk of harm for the individual. The personal preferences of the person to be screened are important to take into consideration throughout this process, as attitudes and decisions about undergoing testing and procedures vary greatly among individuals.

In certain contexts, not present here, screening can be beneficial. Examples where screening can improve the health of asymptomatic individuals at significantly increased risk of disease include hepatitis C, cervical cancer and colon cancer, in appropriate age and risk groups and based on their particular exposures or risk factors. It does not follow that these screening tests would benefit persons not in the specific high risk groups, nor that the tests would possibly benefit everyone.

Yet it is also well-recognized that screening tests have inherent risks and can negatively impact health in serious ways. (NCI, Cancer Screening Overview PDQ) By way of example:

- False positive results are possible.

- False negative results are possible.

- Finding the specific cancer or other specific disease early may not improve the person's health or help the person live longer. There are a limited number of diseases that can be detected early where interventions help the person.

- The testing process with its additional testing and procedures following the screening test, and associated uncertainty and false positives, causes anxiety and other mental health challenges in some persons. (Broderson 2013)

- Additional testing, procedures and interventions that follow discovery of 'abnormal' findings yield minor and major adverse health effects that are most often out of proportion to improvements in health that might occur.

Performing testing in asymptomatic persons that goes beyond the evidence-based recommendations for the specific age, sex, and risk group runs a greater risk of causing serious harms to a person's health with no benefit. In fact, adding more screening tests, or repeating testing at periodic intervals, raises the likelihood of false positive test results and the risk of adverse events associated with procedures and surgery that are part of the cascade of increasingly invasive testing. In the following circumstances, among others, screening is inappropriate or contra-indicated: (i) when the exposure has not been shown to cause the disease according to well-accepted scientific criteria (ATSDR 1995; Hill 1965); (ii) when the disease is rare or not serious or there is no effective treatment or intervention; (iii) when the prevalence of the disease is low or unknown; (iv) when early treatment yields no benefit and/or a significant likelihood of

overdiagnosis; (v) when specificity and sensitivity of the screening tests are not well-documented to be high; and (vi) when the consequences of false positive or false negative tests cause more than modest harm. (Maxim 2014)

Whether testing for a disease can potentially help a person depends on how high the person's risk of disease is, the severity of the potential condition, how well the screening test works, what additional diagnostic testing and procedures would be needed, and whether and how often early treatment can improve health outcomes. There are different types of screening tests that aim to serve as first line testing, before other and more invasive evaluations to rule in or out a disease. In order to reduce the chance of adverse impact, monitoring must be held to well-accepted scientific standards for testing, disease detection, and treatment.

Medical monitoring is distinct from a research study. Medical monitoring is implemented when peer reviewed studies clearly and consistently support causation of a specific disease at the levels of exposure seen among individuals in a given population. (ATSDR 1995)

2. <u>Need for Evidence-Based, Individualized Assessment</u>

Medical monitoring, whether it is part of periodic exams or part of an exposure-related examination, requires a clinician's careful thought process guided by disease recommendations based on scientific evidence—for example, recommendations of the USPSTF and the National Cancer Institute (*see, e.g.,* NCI, Cancer Screening Overview PDQ)—and the individual patient's health profile and tolerance for risk and uncertainty. Specific screening recommendations for individuals are framed after consideration and analysis of numerous personal considerations and the evidence-based guidelines of the USPSTF. It is not consistent with accepted standards of medical care or with principles of disease that a large class of persons with a wide range of exposures, health risks, ages and many other relevant differences would benefit as a whole or individually from a program for medical monitoring for disease based on an exposure.

It is widely accepted as standard clinical practice when evaluating the propriety of medical screening to consider the individual's risk factors for disease, current medical conditions, family history of disease, previous testing, and personal attitudes and concerns about screening and treatment. This allows selection of persons for screening who are deemed to be at high risk for disease and most likely to benefit from screening, thereby avoiding testing and associated harm and worry in persons unlikely to benefit. A medical monitoring program cannot be developed without an understanding of these elements. The steps of testing in the entire screening process for a specific disease are often represented by an algorithm with branching at key decision points. The steps can indicate harms such as the overuse cascade. (Korenstein 2018) For example, **Exhibit C** ("Algorithm - Hematuria Screening for Kidney Cancer and Kidney Disease") describes the steps of testing that can follow a urinalysis, which is a common test used to screen for kidney problems.

The USPSTF has considered individuals' risk factors in depth in its systematic reviews and developed its guidelines specifically for persons at increased risk of a specific disease. The risk groups are based on many different factors such as age, sex, race, ethnic origin, family history, lifestyle factors, pre-existing diseases, and some personal decisions. Furthermore, the USPSTF has recognized the need for individualized assessment, stating that "although evidence is the

primary basis for USPSTF recommendations and statements about preventive services, the decisions made by clinicians for individual patients include other important considerations, such as the patient's clinical state and circumstances and personal preferences, factors that are important to consider when implementing any USPSTF recommendation." (USPSTF 2019) This refers to overlapping spheres of influence in evidence-based clinical decisions. The research-based evidence on testing and treatment is considered in relation to an individual's preferences, an individual's actions and behaviors, and the individual's clinical health status. Developing a medical monitoring plan without utilizing this individual information would disconnect the plan from the individual who is its intended beneficiary. As others in the field of clinical epidemiology and medicine have similarly recognized: "[C]linical decisions must include consideration of, firstly, the patient's clinical and physical circumstances. . . . Secondly, the latter need to be tempered by research evidence concerning the efficacy, effectiveness, and efficiency of the options. Thirdly, given the likely consequences associated with each option, the clinician must consider the patient's preferences and likely actions (in terms of what interventions she or he is ready and able to accept)." (Haynes 2002; *see also* Sheridan 2004; Schrager 2017; Spatz 2016) The primary care practitioner is generally best equipped to implement evidence-based individualized medical monitoring following shared information and decision-making with the individual who is his or her patient.

The ATSDR has acknowledged the importance of these general principles in the specific context of individuals exposed to perfluoroalkyl-related substances. ATSDR is the federal agency within the Department of Health and Human Services that is charged with protecting the health of communities from hazardous substances. ATSDR conducts epidemiologic research, investigates exposures in communities, educates health professionals and communities on the effects of exposure to hazardous substances, maintains exposure registries, reviews scientific studies and provides guidance on monitoring and risk-based communications for the community. Addressing the screening of asymptomatic persons in the context of PFAS exposure, ATSDR concluded that screenings to address perfluoroalkyl-related health risks are not recommended: "For asymptomatic individuals exposed to PFAS, insufficient evidence exists at this time to support deviations from established standards of medical care." (ATSDR 2019) Instead, ATSDR supports using "the same established standards of care they [(clinicians)] would use for a patient who did not have PFAS exposure" and advises clinicians to consider "the patient's overall risk factors, exposure, family history, patient signs and symptoms of illness, and physical examination" in determining appropriate care. (*Id.*) I agree with this position, which is directly at odds with the plaintiff's proposal for class-wide monitoring in this case.

As stated clearly in a treatise on cancer screening by experts at the National Cancer Institute, "[d]etermining the efficacy of screening is a complicated process. Rarely does one size fit all." And further: "Screening is an intuitively appealing activity…In fact, screening is a 'cascade' that can lead to either good or harm. Sometimes screening leads to more good than harm, and sometimes more harm than good. Thus, there is a decision to be made: to screen or not? A process is needed for determining in each situation whether screening is appropriate." (Kramer 1999)

3. Medical Monitoring Criteria

In order to benefit those individuals who undergo testing, and to reduce the risk of unnecessary and harmful testing among healthy persons, medical science dictates that each screening test be evaluated individually with reference to a specific disease in a specific population in which the disease has been studied from an epidemiological perspective. To determine whether the benefits of testing outweigh the harms, certain criteria must be considered. The core criteria listed below are discussed in resources from the National Cancer Institute (NCI, Cancer Screening Overview PDQ), the USPSTF (USPSTF, Methods and Processes), the American Cancer Society (Smith 2019), the World Health Organization (Wilson and Jungner 1968), and ATSDR (ATSDR 1995):

1. Screening must target a specific disease.

2. The hazardous exposure must be known to cause the specific disease.

3. The individual to be screened must be at significantly increased risk of a serious disease as a result of the exposure and must have no symptoms related to that disease.

4. Screening tests for the disease must be reliable and accurate, and the prevalence of the disease must be high enough to justify screening for new cases.

5. The benefits of the full screening and resulting evaluation must outweigh the risks.

6. The clinical outcome must be improved as a result of the screening.

Monitoring is only appropriate where all of these criteria are met. This is the standard and generally accepted approach in medicine and public health.

4. Standards for Identifying Exposure and Significantly Increased Risk of Disease

In situations where a person may have been exposed to substances that may cause an increased risk of future serious disease, it is important to carefully evaluate the exposure and the risk it may pose for a specific disease. The majority of hazardous exposures cause illness and symptoms in the hours and days immediately following an overexposure. Less commonly, exposure to a hazardous compound may cause disease years in the future, such as bladder cancer or asbestos-related lung disease (a latent disease). Where causation between exposure and a latent disease is established, and significant exposure has occurred, consideration of screening options for the latent disease may be a viable option to contribute to improved outcomes, depending on the individual. The individual must have a significantly increased risk of developing the specific exposure-caused disease as a result of the exposure, such that there is a good likelihood of finding the disease through screening. Individuals with similar exposures to a hazardous substance may have different risks of future disease. This is because the timing of exposure during the life cycle varies across individuals. Thus, individuals whose 15-year exposure occurred starting at age 60 could be expected to have different risks than those exposed beginning at age 20. In addition, individuals have other differences relating to genetics, health conditions, diet, tobacco smoking, and other lifestyle factors that impact the risk of exposure related disease.

Screening for disease is not beneficial following most exposures to hazardous substances. Even if an individual is determined to be at high risk of disease, this alone is not sufficient to justify monitoring; the monitoring must also be able to improve and not harm individual health. For example, in a person with a long history of smoking tobacco and asbestos exposure, the benefits of screening for lung cancer may be very limited or nonexistent in comparison with the risks of adverse health impact from procedures and incidental findings and false positives. Thus, screening is often not the best method to reduce disease impact.

ATSDR's guidelines support this conclusion. In order to derive benefit from monitoring, ATSDR has said that those to be monitored must be at a "significantly high risk for the undiagnosed disease (i.e., the disease should have a sufficiently high prevalence in the population)." (ATSDR 1995) By "population" here, ATSDR refers to a defined group that was the subject of epidemiological study and that bears similar characteristics to those who are being considered for testing. Only if the exposure-related condition is present in sufficient numbers of people can screening tests begin a series of evaluations that, in some cases, may lead to diagnosis of the condition being screened for. If the prevalence were high enough—perhaps 1 in 100, for example—then it follows that testing 1,000 people might result in a few diagnoses after some years of monitoring.[3] Some of those diagnosed with the condition might be eligible and accepting of the treatment plan, and some of those treated might see improved health. Unfortunately, those screened and those treated can experience a setback in their health status instead.

In considering who is at high risk for an exposure-caused disease, it is important to evaluate the group or population risk and also to assess the individual's specific exposure and his or her genetic, health, and other personal factors. These factors are important to determine who is at higher risk and whose risk is actually quite low. A key consideration in determining risk of future disease is the level of exposure over time (dose) that a person has received. **Exhibit D** ("What Is Required for Medical Monitoring?") illustrates the considerations that must be assessed in medical monitoring decision-making. Population data from epidemiological studies must be critically reviewed to determine whether the exposure is associated with human disease, and whether exposure can cause human disease. If causation is confirmed, individual factors must also be taken into consideration, including whether the individual's exposure level is known to cause disease, whether there is risk of a specific disease, and particularly from the clinical perspective whether the risk at the exposure level is significantly elevated. "All clinical decisions involve weighing probabilities of benefits and harms for the different options. Population-based studies provide estimates of these probabilities for an average patient, but not for an individual patient with a specific set of characteristics." (Armstrong 2020a) Armstrong has recently described the process of translating population evidence about a specific treatment approach to the case of an individual patient. (Armstrong 2020b) The treatment effect on population outcomes and the absolute and relative reductions in risk are depicted in icon arrays. (*Id.*) The weighing of benefits and harms takes into account the accuracy of the testing; the prevalence of disease and the harms from repeat testing; cascades of testing and the invasive procedures; limited improvement in outcomes due to age and comorbidities; anxiety and mental

[3] The importance of a high prevalence of disease for screening can be explained with examples from different testing scenarios. Where screening has been recommended, the reported prevalence among populations that undergo screening tests ranges from 0.05 to 0.9, mostly at the upper end of that range. (Maxim 2014)

health impacts of screening; and the potential for early treatment to affect outcome. As a final step in assessing the benefits and harms, the individual must understand the potential impacts and decide whether the monitoring and associated testing and treatment are worthwhile. If the evidence and/or the individual's preferences do not support monitoring for exposure-related disease, then the individual continues to receive periodic screening based on their age and risk factors, as detailed by the USPSTF.

Until about 30 years ago, it was commonly believed that routine testing such as blood counts, chemistry panels, urine tests, and chest x-rays would result in screening-related health benefits for most people over a certain age and for those being admitted to the hospital. (Schwartz 2004) With additional clinical studies, the medical community has shifted away from the thinking that, as a rule, the more tests administered, the healthier everyone will be and the longer everyone will live. (Kramer 2000a) Today, an extensive evidence base has established that performing a routine battery of screening tests on asymptomatic persons subjects many healthy persons to potentially harmful interventions and repercussions from testing, inaccurate results, and diagnostic procedures, and does not improve the population health. (*See, e.g.,* Croswell 2010; Kramer 2009; Malm 1999)

Plaintiff Fails to Address the Risks of Class-Wide Medical Monitoring

The plaintiff embraces the view of 30 years ago and assumes—without qualification—that plaintiff's proposed medical monitoring and analysis program will benefit all members of the proposed class. In doing so, however, he gives no consideration to the myriad individual differences between class members, including differences in their exposures, medical histories, family histories, lifestyle factors, and other unique characteristics. Well-established scientific and medical principles require that such factors be considered in assessing the need for monitoring and determining the type of monitoring that is appropriate. Moreover, plaintiff's disregard of individual differences ignores the medical community's recognition that medical monitoring itself poses significant dangers to individuals and therefore requires a case-by-case assessment in order to determine whether the potential benefits of screening for a particular disease outweigh the serious risks.

Experience has taught us that health outcomes do not necessarily improve in response to a medical monitoring program. Testing is not "risk free." In fact, harms often result unless there is careful consideration of individual factors and potential benefits and harms in advance. For example, a person without symptoms who initiates a screening for kidney disease with urinalysis may have substantial further evaluation for blood in the urine, protein in the urine, or sugar in the urine, just to name a few possible findings. Each of these findings can then initiate a series of additional tests and procedures in order to determine whether there is a disease causing this finding and whether early treatment is beneficial or not. Blood in the urine may relate to a brief urinary tract infection, but the evaluation will likely extend to tests for kidney function, blood clotting, anemia, ultrasound, and cystoscopy and more. *See* **Exhibit C** ("Algorithm - Hematuria Screening for Kidney Disease and Kidney Cancer").[4]

[4] The algorithms in **Exhibits C and E** illustrate the stepwise cascade of testing and evaluation that are often inherent to the testing process. Each of the tests, scans, and procedures has risks, which can include physical harm, overdiagnosis, false positive and false negative results, and psychological reactions such as anxiety. The algorithms,

Screening for disease can result in health problems either related to the screening tests or resulting from the testing and procedures performed when the initial screening test is positive. (Malm 1999; Harris 2014) A positive test may indicate a finding that turns out to be a false positive. Yet false positive tests generally lead to additional investigation, since it cannot be known at the time that it is not a true positive.

An abnormal test result, whether true or false positive, often leads to a battery of testing including some invasive procedures. Each subsequent procedure carries additional risks of harm. Overdiagnosis (the diagnosis of a condition that will never become clinically apparent) and overtreatment (medical interventions that are not warranted because the patient is better off without treatment) are important adverse outcomes that may occur with screening, especially when testing is not done according to evidence-based guidelines. (Hofmann 2017; Ebell 2015a; Ebell 2015b) The inability to distinguish cancers that would have gone away or never caused symptoms if left untreated affirms the need to carefully consider the proposed initial monitoring plans that may lead to findings (*e.g.,* on radiologic scans) that are more likely to hurt than to help advance the health of the screened person. Overscreening is well documented to have serious adverse impacts, such as heart failure following cardiac angiography (Schmidt 2016), and tests interpreted as abnormal that cause a great amount of worry.

Even testing that is planned with good intentions may subject a patient to unnecessary medical risks and discomfort, as well as anxiety. Adverse events related to testing often occur with greater frequency than the frequency with which latent diseases are detected and effectively treated. Certain harms occur more frequently when screening tests are performed in persons at low risk for the condition.

At a population level, the low risk of an individual equates to low prevalence of disease, and low prevalence translates to low positive predictive value and a high rate of false positive results. Using a test with low positive predictive value will rarely, if ever, provide benefit to the screened person(s). For example, if an ultrasound of the abdomen is performed on someone without a high risk of a specific abdominal disease—such as a healthy 40-year-old woman—the scan is more likely to reveal findings that are not clinically important (but may require further evaluation to know that) than to result in a diagnosis of an unrecognized asymptomatic disease process for which treatment will improve the future outcome for the individual. Liver enlargement, possible bile duct widening, a thickening of the bladder wall, or possible enlarged lymph nodes may be identified on the ultrasound on the 40-year-old woman in this example. None of the above may be seen on further evaluation (false positive incidental findings). Even if true pathology were found (such as thickened bladder wall due to urinary tract infections, not cancer), there may be little or no prospect for improved future health.

Other examples of adverse effects include: (i) bleeding from the liver when performing a diagnostic liver biopsy after screening liver enzymes that leads to other tests and then to a nondiagnostic CT scan that shows possible nodules and possible early cirrhosis; (ii) persistent bleeding and pain following prostate biopsies after a high PSA test result; and (iii) an adverse

as shown, do not represent the only or best evaluation. Rather, they demonstrate the need to consider the consequences of testing and tailor a testing plan to the individual patient's needs, risks, and preferences.

reaction to anesthesia during a cystoscopy to evaluate the cause of blood in the urine found during routine testing.

Medical testing not infrequently results in uncertainty, mixed data, unclear diagnosis, and/or the need for longer term evaluation and ongoing testing, with increasing levels of anxiety. The results, even after follow-up testing and procedures, may bring no conclusive answer regarding whether disease is present or not. Examples include breast cancer (for example, diagnosis of ductal carcinoma in situ and lack of clarity about future risk and need for treatment), prostate cancer (high PSA and repeated biopsies inconclusive for cancer), and liver disease (markers such as liver function tests can be abnormal, but the possible causes are many and additional and even extensive testing may not result in a clear explanation and treatment plan). Certain medical screenings can and do improve the health of specific populations, and this translates to benefits from screening for some individuals. Evidence-based screening recommendations include colon cancer screening for those over age 50, periodic blood pressure checks and assessment of cardiovascular risk in adults over age 40, and periodic testing for cervical cancer in women in certain age and risk groups. Individuals with a genetic risk identified by family history or genetic testing may receive more frequent testing or additional screening measures, where relevant, if the person screened agrees with additional testing at periodic intervals. These specific screening programs are examples that have been well-studied in large populations of people and shown to offer the potential for improving health outcomes (mortality and morbidity) when applied to persons in specific risk groups in the general population and when the additional diagnostic testing is performed and treatment is given. (USPSTF, A and B Recommendations) This is in contradistinction to a broad-brush approach to monitoring, where scientific evidence does not inform the selection of tests; a specific disease is not known to be caused by actual exposure doses and exposure at any level may not cause the disease; specific disease entities are not known to be caused by actual exposure doses, and perhaps not even identified; the target age and risk groups are not specified; and the disease risk is not quantified for different exposures and risk groups. Persons at high risk of a specific exposure related disease – if they are documented to occur – may benefit from screening, but the full analysis of the potential benefits and harms must be carefully considered before defining a group and program for medical monitoring. (See **Exhibit D**)

Persons who are elderly, already have advanced disease, and/or complex co-morbidities are far less likely to benefit from monitoring for future disease and thus would not usually be subjected to mammograms, colonoscopy, or similar screening tests. (Causada-Calo 2020; American Cancer Society 2019) Screening is often not recommended (i.e., for cancer) for adults older than 75 years of age because current evidence suggests that harms outweigh the benefits for that population. (American Cancer Society 2019) For similar reasons, persons in their 60s or younger who have serious comorbid conditions or would be high risk for life threatening complications from the treatment or surgery are not recommended for screening.[5]

[5] See, for example, USPSTF's breast cancer screening, which is recommended for women under age 75 who meet certain criteria. (USPSTF 2016) Stopping screening should be considered for "women aged 70 to 74 years with moderate to severe comorbid conditions that negatively affect their life expectancy" because they "are unlikely to benefit from mammography. Moderate comorbid conditions include cardiovascular disease, paralysis, and diabetes. Severe comorbid conditions include (but are not limited to) AIDS, chronic obstructive pulmonary disease, liver

If someone is at high risk from surgery or otherwise not a good candidate for or accepting of evaluative and therapeutic interventions that would follow, then shared decision-making would involve discussing whether there is a rationale for screening or not. Shared decision-making is the process whereby clinicians and patients discuss the best available evidence regarding clinical decisions, and patients are encouraged to consider the clinical options and how those options fit with their personal preferences. Shared decision-making is now widely endorsed in clinical care settings, similar to the informed consent process. (Armstrong 2020a; Schrager 2017) Shared decision-making calls for a bidirectional flow of information that involves the patient providing his or her thoughts and values, and together he or she and their healthcare providers making a decision. (Schrager 2017)

A central tenet of shared decision-making is that patients have a right to understand the harms and benefits of different options (including screening for liver disease or not screening, for example) before proceeding with a testing or treatment intervention. Patients are then better prepared if they encounter complications and/or sequential testing, many false positive or indeterminate results, and great anxiety. (Morgan 2020) The possible benefits and harms of each test and the steps that follow may affect patients differently. The discussion about downstream tests and risks is critical for a person to decide whether the potential upside is worth the potential downside of testing. Shared decision-making is the opportunity for a patient to bring his or her personal values and preferences to the decision-making, which usually involves uncertainty and tradeoffs. When patients participate in shared decision-making, they are more likely to follow through on testing and evaluations and treatment. (National Learning Consortium 2013) Patients prefer to be engaged in decisions, and, when they are, they have better experiences and adhere better to the management plan. (Schrager 2017; Sheridan 2004) However, the plaintiff does not explain how, if at all, his medical monitoring would use shared decision-making as part of the initial conversation before people undergo testing or how he would ensure that each person understands in advance the full extent of possible downstream tests and complications in the context of that person's priorities and likelihood of benefiting.

Undergoing age- and sex-appropriate evidence-based screening evaluations does not ensure that any specific *individual* will benefit from the screening. Indeed, the health of some persons will be set back. The major determinants (beyond disease and testing factors) of how beneficial the evidence-based screening will be are: the individual's medical history, current and active diseases, overall state of physical and psychological health, and personal preferences regarding testing and intervention. (Harris 2014; Eckstrom 2012) As these examples illustrate, personal and individual considerations must be part of the development of a monitoring plan from the beginning.[6]

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disease, chronic renal failure, dementia, congestive heart failure, and combinations of moderate comorbid conditions, as well as myocardial infarction, ulcer, and rheumatologic disease." (*Id.*)

[6] In the case of screening tests for prostate cancer, for example, a clinician would share with the patient the test process, which begins with a PSA blood test and then proceeds to scans and biopsies if the PSA results are not in the range of population norms. The likelihood of finding a prostate cancer that, if treated, would result in better health outcomes than if found later or never found depends on individual risk factors including genetics, race, age, weight and diet; the extent of discomfort and harms related to procedures such as multiple biopsies; the follow-up testing and procedures that would likely be recommended if the results were indeterminate and the complications related to those; and the harm and benefit of surgical treatments that may cause permanent serious dysfunction. Prostate cancer is a disease that is often overdiagnosed, meaning that in many cases the disease will not cause illness or death in the

Those with chronic disease or multiple comorbidities are more likely to suffer harms from screening, diagnosis, and treatment. Older persons are especially susceptible to adverse outcomes from testing and overdiagnosis. The value of screening can even differ markedly for two individuals of the same age. (Eckstrom 2012; Schapira 2016) Screening is not a one-size-fits-all medical evaluation process. People should not be included in medical monitoring for disease when they have no or little chance of benefiting from reduction in severity of the disease years in the future.

The harms of screening tests include inaccurate results (false negative and false positive), psychological harm from disease labeling, overdiagnosis of disease (finding a cancer that was unlikely to become clinically apparent during the patient's lifetime in the absence of screening), and the harms of disease treatment. (Feldman 1990; Huo 2019; Brodersen 2013) With respect to cancer specifically, the National Cancer Institute describes the potential harm and benefit of screening and early detection as follows:

> Some patients whose cancers are detected and treated early may have better long-term survival than patients whose cancers are not found until symptoms appear. Unfortunately, effective screening tests for early detection do not exist for many cancers. And, for cancers for which there are widely used screening tests, many of the tests have not proven effective in reducing cancer mortality.
>
> . . .
>
> Importantly . . . in addition to benefits, screening has downsides. In particular, there are the risks of overdiagnosis and overtreatment—the diagnosis and treatment of cancers that would not threaten life or cause symptoms.
>
> . . .
>
> Overdiagnosis and overtreatment expose patients unnecessarily to the potential physical harms of unneeded and often invasive diagnostic tests and treatment, as well as to the psychological stresses associated with a cancer diagnosis. (NCI 2018)

It is a serious matter to subject many non-symptomatic persons to testing in order to try to reduce the risk of future disease in a few people. Everyone tested is subject to the full range of possible harms—many will have false positive results, indeterminate results, anxiety, invasive procedures with and without complications, and some will end up worse in terms of health than where they started. A particularly challenging aspect of medical monitoring, for patients, is living with

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person whether detected and treated or not. Individual preferences and the need to understand the full scope of testing and procedures and treatments at the outset are critical to making an informed decision about doing the initial PSA screen. Visual aids are often used to explain to patients the cascade of testing and risks and the points where decisions need to be made. The clinician would also explain what else may be seen on scans that might suggest further evaluation in other organs and lead to a cascade of testing separate from the disease being targeted for screening. Information shared would include the likelihood of diagnosing prostate cancer that could be effectively treated in this patient; the range of side effects and complications that could occur; and the chances that evaluation might leave uncertainty in the diagnosis and/or prognosis that could undermine the treatment option. The values and preferences of the patient are an integral part of the discussion about these considerations.

uncertainty—for example, having to accept indeterminate answers after biopsies—and the impact that this has on emotional health. (Schapira 2016)

False positive results are known to be common in most screenings, and false positive results often create difficult choices and result in several types of physically harmful outcomes. (Korenstein 2018; Croswell 2009) False positives are a more frequent occurrence if the test has a low specificity for the disease and if the disease does not occur at a high enough rate in that population to find persons with the disease. An example of screening with a high risk-benefit ratio is the performance of a screening test in young persons (for example, a urinalysis to detect renal cancer) when the disease occurs exclusively or almost exclusively in adults or older people.

False negative results can occur with any test but are more common with tests that have a low sensitivity for the disease in the population tested. For example, a test with 80% sensitivity misses 20% of persons who actually have the disease. Those persons presumably think that they have been given a clean bill of health, and may behave differently, including being less likely to readily report symptoms to a doctor or make a routine visit, believing they know they do not have the disease.

An example of a test with a low negative predictive value is liver function tests within normal range. Serious liver disease including steatosis and non-alcoholic fatty liver disease may be present when liver function tests are entirely normal. In the presence of liver cancer or a mass in the liver, a person may have normal liver function testing results. (Sheka 2020) Thus, liver function testing can provide false reassurance and dangerous misinformation, as well as commonly causing overtesting and overdiagnosis because of frequent false positive results. In older persons or persons with limited life expectancy, screening tests are more likely to result in overdiagnosis and overtreatment, with resulting negative impacts. (Black 2000; Davies 2018; Ebell 2015a; Ebell 2015b)

The plaintiff's proposed monitoring program would subject persons to unnecessary testing to no advantage, while raising the risk of various adverse outcomes.

Many tests, especially those performed on large numbers of people, have high false positive rates because they have low specificity for a specific identified disease. This means that many persons may register as abnormal on a screening test and may still not have "normal" results on follow up tests, despite not having the disease being screened for. For example, liver function tests are nonspecific and they can be high (abnormal) in almost any minor liver disease or even after drinking alcohol without liver disease, and the tests can be abnormal with celiac sprue and muscle diseases, among other diseases, and in some persons taking medication including antibiotics. (Pratt 2000) Therefore, while the potential for finding liver disease would be vanishingly small, the potential for false positive results would be very high. Examples of screening for disease where the tests often register abnormal in many persons, including those without the disease, include an EKG, blood tests for ovarian cancer, blood tests for thyroid cancer, and blood tests for prostate cancer. Other tests such as physical examination and scans to look for disease can often show abnormal results in persons without disease.

Another example of a test with low specificity is a urinalysis performed as a potential means to screen for renal cancer and renal disease. The steps involved in medical evaluation after finding

blood in the urine are an example of the hazards associated with what begins as a simple medical test. A urinalysis is a test of multiple different components (protein, cells, blood, osmolarity, etc.), and an abnormal value for any of these components can be associated with various medical conditions. Multiple further tests are therefore likely if any part of the urinalysis is abnormal. Blood in the urine (hematuria) is one possible finding of the test, which may relate to a variety of conditions, only one of which is the presence of kidney cancer. An algorithm can demonstrate the steps for evaluation of hematuria and the bifurcations for decision-making. *See* **Exhibit C** ("Algorithm - Hematuria Screening for Kidney Disease and Kidney Cancer"). These steps might include: urinalysis reveals hematuria; check for red blood cells; repeat urinalysis, perform urine culture, pregnancy test, CT scan, and/or abdominopelvic CT with and without contrast for urography; and refer for cystoscopy. Each step narrows down the possible underlying causes of the hematuria and provides new information to aid in determining the next step and the likely diagnoses. If no disease or explanation is found, the recommendation may be to repeat a urinalysis each year. Along the way, each step creates the potential for positive findings that may be true or false positives.

When one considers the array of findings that can be detected at each step, the cascade effect becomes apparent. For example, while the purported goal of the urinalysis originally may have been to screen for renal cancer, a finding of hematuria may lead to other unrelated findings. Kidney stones may be seen on a subsequent scan following the urinalysis, but that does not mean that the stones are responsible for the hematuria. The whole evaluation is far more likely to find urinary tract infections and other common asymptomatic conditions, or find nothing at all, than to detect asymptomatic chronic renal disease or cancer. Even when a small renal mass is detected, the diagnosis is far from clear, and there are many nonmalignant causes that need no intervention. A small renal mass may be a benign renal tumor—for example, oncocytoma, angiomyolipoma, or metanephric adenoma—or metastatic disease, lymphoma, renal abscess or focal pyelonephritis (infection). A renal biopsy or aspiration is then performed. There are significant risks associated with either a percutaneous biopsy or an open biopsy and surgery. Some findings may be difficult to characterize on the scan, and a biopsy may yield indeterminate results. In addition to the emotional impact and the risks of surgery, immediate and late complications may include compromised renal function.

With recurring or periodic monitoring, for example annual urinalysis testing, regular imaging will further increase the risk of other miscellaneous findings of unclear significance. Each time a scan is performed, masses or other possible abnormalities, called incidental findings, may be seen in the ovaries, lymph nodes, bladder, spine, aorta, etc. These findings, though not part of the intended screening process for a certain disease, often lead to more extensive, painful, and invasive testing and complications. Incidental findings can lead to additional cascades of testing and treatment and may cause harm without clinically meaningful outcomes. (Ganguli 2019; Mandrola 2019) A first-hand account of sequential testing and pain and complications with routine screening for colon cancer is described by Casarella (2002).

The negative impact of the cascade of medical testing—which occurs once monitoring is initiated and there is a positive result for any test—is made worse by failing to understand the likelihood of false positive tests, by overestimating benefits and/or underestimating risks, and by arriving at an ambiguous conclusion. (Deyo 2002) Better education of patients and full discussion of the cascade of testing in the patient-physician encounter can help reduce the

emotional toll. Some patients, once informed about risk and benefit, opt not to undergo the screening. The plaintiff does not discuss the overuse of screening tests, and he has not identified a plan to convey a scientifically accurate understanding of harms associated with overused testing by incorporating shared decision-making. (Moyer 2012; Elwyn 2017)

Screening modalities are associated with other risks too, including cancer associated with radiation from x-rays, CT scans, and other radiologic procedures. The American Cancer Society (ACS) has summarized epidemiologic data on cancer risks associated with diagnostic procedures such as lung CT, mammography, and CT colonography. The ACS concludes that the best way to reduce the risk is to ensure the widespread use of evidence-based criteria for making decisions about the appropriateness of testing. (Linet 2012) The plaintiff does not present any evidence-based criteria for making risk-benefit decisions for the persons who may undergo monitoring.

A high rate of complications will ensue following monitoring that is inappropriate and thus not designed to benefit the specific individuals with known and significantly elevated risk for the future disease and with any other preexisting conditions known and taken into account. The occurrence of organ damage, bleeding, impairment of function, pain, and other adverse outcomes are unacceptable outcomes for people who had no symptoms or signs of disease and simply set out to screen for and prevent potential future problems. (NCI, Cancer Screening Overview PDQ) There is no question that the harms will greatly outweigh the benefits if medical monitoring is undertaken on a class-wide basis to find an array of conditions among all proposed class members.

Even plaintiff agrees that one would need to know what the risks and benefits of testing are, and that deciding what tests make sense for a person is a personal decision made by the patient and his/her doctor. (Hardwick Dep. Tr. at 238-241) This is directly at odds with the one-size-fits-all approach that plaintiff seeks in this case.

Plaintiff Assumes All Proposed Class Members Are At Increased Risk

Before proposing any form of medical monitoring, plaintiff should have undertaken an analysis of whether the individuals that he proposes to monitor are at a significantly increased risk of a particular disease as a result of their exposure. ATSDR has opined that "[t]he risk of adverse effects depends on several factors, including the exposure dose, the frequency of exposure, the route and duration of exposure, and the time of exposure during the lifecycle (e.g., fetal development, early childhood)."[7] (ATSDR 2019) Yet the plaintiff makes no attempt to assess the exposures of individual class members and the relationship of those exposures to specific diseases, simply maintaining instead that every class member who has at least 0.05 ppt or more of PFOA and 0.05 ppt of any other PFAS chemical in their blood is at equivalent very high risk for varied (yet unspecified) diseases and for each person the harms are outweighed by benefits of screening to find the disease early and treatment to improve survival is available and acceptable.[8]

[7] ATSDR further explains, "Health risks associated with PFAS are not specific to PFAS exposures. These health risks are also influenced by many other environmental, social, or genetic factors." (ATSDR 2019)
[8] The problematic nature of this general and vague assertion is furthered by the fact that PFAS are found throughout the environment. People are exposed daily through sources including carpets, furniture, clothing, food, and indoor dust.

ATSDR, the federal agency that focuses on hazardous exposure and community health, has carefully studied the communities where high levels of PFOA have been found in drinking water. Its scientific based conclusions are directly opposite to plaintiff's unsupported assumptions. In its report "An Overview of the Science and Guidance for Clinicians on Per- and Polyfluoroalkyl Substances (PFAS)," ATSDR concludes, "There is no established PFAS blood level at which a health risk is expected, nor is there a level that predicts health problems." (ATSDR 2019) In the same document ATSDR says that clinical decisions for PFAS-exposed persons should be based on the patient's individual risk factors. This is further evidence that for a community group there is no exposure-related action to be taken and no defined risk of future disease.

Further, plaintiff's proposed threshold dose (0.05 ppt or greater in blood) is particularly problematic, because there is absolutely no evidence that this exposure level puts any person at any risk, let alone significantly increased risk, for any adverse health effect.

Notably, every regulatory agency that has set regulatory guidelines for PFAS exposure, including ATSDR and EPA, has set a safe level for drinking water that would result in a substantially higher blood level than the level being used to define the class in this case. This is quite telling, as regulators set limits to be protective, selecting guidance values, based on conservative assumptions and safety factors, that are not expected to pose a risk for adverse health effects for even the most sensitive individuals. And yet, plaintiff assumes that exposures even a fraction of the regulatory levels place everyone at significantly increased risk for a range of adverse health effects.

It is also inappropriate for plaintiff to apply the same threshold dose to all diseases to be monitored. As ATSDR counsels, each specific adverse health effect must be considered individually when contemplating medical monitoring. (ATSDR 1995) So even if 0.05 ppt were a threshold dose for a significantly increased risk for a particular health endpoint (which it is not), that does not mean that it would be a threshold dose for other endpoints or diseases.

It is important to put plaintiff's proposed class into context. The National Center for Health Statistics has an ongoing survey, the National Health and Nutrition Examination Survey (NHANES), to study the health and nutritional status of U.S. adults and children. Blood PFAS levels have been measured as part of NHANES since 1999. As documented by NHANES, blood PFAS levels have been steadily declining in the U.S. general population over the past few decades. Using the most recent NHANES data from 2015-2016, the average blood level in the U.S. general population was 1.56 part per *billion* (ppb) for PFOA, 4.72 ppb for PFOS, and 1.18 ppb for PFHxS. (ATSDR 2019) As defined in plaintiff's motion for class certification, the medical monitoring class would include anyone with a blood level of PFOA of 0.05 parts per *trillion* (ppt) and a blood level of any other PFAS of 0.05 ppt. 0.05 ppt is the same as 0.00005 ppb. In other words, plaintiff is proposing to include in the medical monitoring class anyone with an exposure level more than 10,000 times lower than the national average. This would essentially include everyone in the entire U.S. population.

No scientific organization has concluded that *any* screening is necessary for people with *any* level of PFAS exposure, let alone that screening is necessary or advisable for *everyone* in the U.S. Indeed, as noted above, ATSDR has concluded the opposite of what plaintiff proposes. No

health organization such as the National Cancer Institute, American Cancer Society, USPSTF, or the American Nephrology Association has recommended such screening.

Population-based medical monitoring requires identification of a specific population that, by virtue of its exposure, is at significantly increased risk for specific diseases as compared to the general population. If the proposed population for monitoring is the general population—as is proposed here—then, by definition, it is not at significantly increased risk compared to the general population, and special monitoring is not warranted.

Plaintiff Fails to Consider Important Individual Factors and Medical History That Differentiate the Proposed Class Members

The plaintiff's proposal for medical monitoring further fails to comport with well-established screening criteria and principles of medical monitoring because it lacks any consideration of the proposed class members' individual risk factors and medical histories. Medical monitoring for disease depends on understanding evidence at a population level and then making decisions on an individual basis related to the specific person and situation. (Armstrong 2020b) **(See Exhibit D)** Rather than advise an omnibus screening program for all patients exposed to PFAS (like the one the plaintiff proposes), ATSDR emphasizes the need for individualized assessment: "Care of a patient exposed to PFAS may be considered based on the patient's overall risk factors, exposure, family history, patient signs and symptoms of illness, and physical examination." (ATSDR 2019) The guidance warns that "[s]ome of the testing for PFAS-related health concerns have risks and are not generally performed on patients showing no signs or symptoms of illness" and for this reason care must be based on an individual's "overall risk factors, family health and environmental exposure histories, and any signs and symptoms of illness." (*Id.*)

The proposed class members will have numerous individual risk factors for different diseases. Factors that predict risk for complications from the screening tests and the cascade of further scans and procedures would also vary among the class members. These factors must be considered in developing a plan to use screening tests that aim to diagnose disease early in order to improve future quality of life and longevity. Moreover, the likelihood of experiencing a positive health outcome after medical monitoring is dependent on a range of factors including individual variables relating to exposure and risk of disease, current health conditions, past medical history, and life expectancy.

First, as noted above, proposed class members will differ significantly in their exposures. This is because numerous factors specific to individuals influence exposure to PFAS, for example: amount of water ingested per day; percentage of daily water intake coming from various water sources (municipal water supply, private well, bottled water, water supplied at work as opposed to at home, etc.); duration of use of contaminated water supply; time in life cycle of consumption; and the myriad other potential sources of exposure beyond drinking water. Given the exposure threshold component of the proposed class definition, we know for a fact that there would be tremendous variation (multiple orders of magnitude) in the PFAS blood levels of potential class members, meaning that Mr. Hardwick's PFAS exposure cannot be representative of the larger class, and that the class as a whole does not represent a cohesive group in terms of exposure.

In addition to these variations in exposure, among the proposed class members there will be a wide range of medical conditions, underlying health risks for future disease, lifestyle factors and many other individual factors affecting the benefits, harms and personal decisions regarding medical monitoring.

Mr. Hardwick's medical records and his statements related to health in his deposition show he is not representative of the potential class. [redacted] His specific exposure history to PFAS (e.g., use of AFFF and firefighting gear potentially containing PFAS) also differentiates him from other potential class members, as do his water consumption patterns and practices.

Other class members will have one or more active diseases, or no disease, as well as specific factors relating to diet, exercise, weight, tobacco smoking, medication use, family history, and other personal factors relating to future disease, all of which can and do impact the risk and benefits of doing medical screening tests. Some proposed class members will already be receiving tests that would be included in a medical monitoring program. [redacted] In his deposition he says that he is not interested in additional monitoring tests.

Mr. Hardwick differs from other potential class members with respect to factors that are important in designing and implementing screening for future illness. Class members would differ significantly in terms of (at the very least) genetic factors and past medical history, lifestyle choices, occupational history, and current state of health. Understanding their level of functioning and their attitudes about screening, medical procedures, testing, and acceptance of uncertainty is important and would require more information from individual medical consultations.

Significantly, the plaintiff also makes no attempt to distinguish between adults and children in describing the medical monitoring program he suggests. A variable as simple as age has a major impact on screening. Children are less likely to be at risk for some diseases. They will, however,

be likely to have false positive test results that require evaluation. They can also have other complications. In addition, screening children for diseases that occur in middle age and beyond raises anxiety among the children and their parents and might discourage them from seeking preventive medical services and medical care in the future. Conversely, there are likely to be many elderly residents in the proposed class, and these individuals will be less likely to see benefit. Instead, they are more likely to suffer physical and psychological complications from screening tests. (Eckstrom 2012)

Knowledge of the individual differences among the proposed class members is critical to assessing their risk of disease and designing testing that will minimize harm. As discussed here, the wide variation among the proposed class members in terms of exposure dose, age, gender, genetic and lifestyle risks for disease, past medical history, occupational history, pre-existing conditions and current diseases, functional status, life expectancy, screening already done, mental health, and attitudes about prevention and undergoing tests all impact the success of monitoring for future disease among these individuals. Personal factors—such as those discussed through shared decision-making, relating to attitude, adherence, resiliency, and mental health—also contribute to the chances of success of monitoring. These differences do not permit a class-wide approach to medical monitoring where the goal is to improve health outcomes.

Plaintiff Fails to Define the Monitoring He Proposes and Fails to Establish that Any Disease Endpoints Are Appropriate for Medical Monitoring

To develop a medical monitoring program, specific features must be defined in order to know that the testing can and will benefit the participants. The plaintiff must specify the number of participants, the precise diseases to be monitored for and what tests will be utilized at what frequency; the sensitivity, specificity, and positive predictive value of proposed tests; and the likelihood of finding disease earlier than under normal circumstances, at a treatable stage, and with an improved clinical outcome on the natural history of that disease. For each step in the screening cascade the potential harms must also be delineated, including negative physical and mental health consequences of testing and early treatment, false positive testing, false negative testing, overdiagnosis, and overtreatment. The potential harms will be additive during each screening over the years during the duration of the proposed monitoring and must be weighed against the likelihood and potential benefit of diagnosing the specific disease when interventions could make a positive difference. Without specifying these and similar components at the outset, the plaintiff cannot even make a plausible or colorable claim that monitoring would reduce disease burden and improve health outcomes among individuals who undergo screening. Such a proposal violates the fundamental principles that the scientific community assesses in determining whether and how to employ medical monitoring.

Moreover, the literature does not support a finding that any conditions are causally related to exposure to any PFAS level or that outcomes would be improved by screening for those conditions. As stated previously, one of the threshold requirements for an exposure-based medical monitoring program is the establishment of a causal relationship between such exposure and the development of specific diseases in humans. Here, that threshold requirement has not been met. A large number of epidemiologic studies have examined the relationship between PFAS exposures and a variety of cancer and non-cancer conditions. But, as ATSDR has noted as part of its extensive review of the existing evidence, causation of human disease has not been

documented, in part because most studies are cross-sectional, and these do not permit evaluation of causation. (ATSDR 2018) In a cross-sectional study, data are collected on the whole study population at one point in time. This provides a snapshot of the population and can be used to describe characteristics, but it cannot determine cause-and-effect relationships, in part because a single snapshot offers no indication whether exposure preceded disease in any of the diseased patients.

Three different populations have been included in the epidemiologic studies regarding PFAS: workers at facilities involving the manufacturing or use of PFAS, residents in communities situated near a PFAS manufacturing site and with elevated levels of PFAS in drinking water, and residents with background levels of PFAS. The exposure levels considered in those studies varied greatly across these three groups. Even among workers at PFAS production plants, who had blood PFAS levels in the thousands (mcg per liter), there was no reliable evidence of increased disease or mortality, after monitoring for years, even decades.

The ATSDR conducted a multi-year in depth review and analysis of animal and human studies of health effects related to perfluoroalkyl exposure, resulting in a comprehensive report over 800 pages long. (ATSDR 2018) This report from ATSDR was also peer-reviewed by other governmental agencies, including the U.S. EPA, as well as a number of external experts. The report identified "possible" associations between perfluoroalkyl exposure (a broad category of chemicals) and increases in liver enzymes, increases in serum lipid levels, pre-eclampsia, thyroid disease, and several other conditions. However, ATSDR clearly stated that causation has not been established between PFAS exposure and any adverse health effects in humans, that the available studies are inconsistent in their findings of associations, and that the associations seen in some studies may not be biologically relevant. (*Id.*) I have reviewed the ATSDR report and agree with the above stated conclusions. In addition, more recently, ATSDR advised clinicians that, "[f]or asymptomatic individuals exposed to PFAS, insufficient evidence exists at this time to support deviations from established standards of medical care," and even "[f]or patients with signs or symptoms of disease, clinicians can treat these patients using the same established standards of care they would use for a patient who did not have PFAS exposure." (ATSDR 2019)

ATSDR, after years of extensive and thorough analysis of this very issue, has expressly concluded that (1) causal relationships "have not been established for any" adverse human health effects from PFAS exposure (ATSDR 2018); (2) no medical screening beyond standard medical care is warranted for people with PFAS exposure (ATSDR 2019); and (3) any PFAS-related medical testing should be based on individual factors (ATSDR 2019). An early epidemiologic study of 69,030 persons conducted as part of a settlement in a different legal case examined communities living near manufacturing facilities and found evidence suggestive of association between PFOA exposure and six diseases (the Leach Science Panel Work). However, under the parameters of the controlling legal settlement, the Leach Science Panel only sought to identify "probable links"— not causal relationships—between PFOA exposure and disease. (*See* Aug. 2, 2005, Jan. 22, 2010, and Jan. 24, 2010 Letters from C8 Plaintiffs' Counsel to C8 Science Panel) A "probable link" is different from, and does not rise to the level of, causation. (*Id.*) As recently as December 2019, the ATSDR likewise recognized that "the evidence does not establish a causal relationship between PFAS exposure and disease." (ATSDR 2019)

Additional studies performed have, in some cases, reported associations with some of the same and other diseases identified by the Leach Science Panel Work. Yet the associations are not consistent among human studies, and no causal relationship has been established. For example, in the case of elevated liver enzymes, the elevations were small and not believed to be clinically important. (ATSDR 2019) Results of studies on cancer were not consistent either, and most did not control for other risk factors such as smoking. Chance, bias, and confounding and small numbers may limit the conclusions.[9] Most recently, in October 2020, Leach Science Panel members and other scientists reviewed the scientific studies on PFOA exposure and human disease, concluding that "overall the epidemiological evidence remains limited." (Steenland 2020)

To highlight just some of the important flaws in the plaintiff's suggested approach to medical monitoring, presented below are three examples of diseases with considerations related to the natural history, the epidemiologic data and causation by PFAS, and the criteria for medical screening – all of which are important in planning and implementing a medical monitoring program to benefit persons at high risk of disease.

1. Kidney Cancer

Renal cancer includes various different forms of malignancy involving the kidney, including renal cell cancer, urothelial cancer, cancer of the renal pelvis, sarcoma, Wilm's disease, and lymphoma. These are entirely different disease processes, each with a different pathology, disease course, approach to treatment, and prognosis. Some renal cancers do not spread and behave more as benign diseases, whereas others have variable potential for aggressive spread. Wilm's disease is more common in childhood. Thus, there are different approaches to screening for renal cancer depending on the disease targeted and the target population. The specific disease would have to be identified, and the monitoring program set up with that disease as the endpoint. The program would have to identify a specific renal disease that PFAS causes at low community exposure levels, and there would have to be sufficient cases identified in the community so as to offset the harms for the other participants, some of whom would experience extensive testing and uncertainty. *See* **Exhibit C** ("Algorithm - Hematuria Screening for Kidney Disease and Kidney Cancer").

Persons in the proposed class have different risk factors and are not all at the same or similar risk for developing kidney cancer. Important risk factors for kidney cancer are tobacco smoking, obesity, older age, a high fat diet, high blood pressure, certain medications, cadmium exposure, genetic factors, and chronic kidney disease. Even for those persons with risk factors, there are no recommended screening tests for kidney cancer for people in the general population. (American Cancer Society 2020b; American Society of Clinical Oncology 2019) Persons who have certain inherited conditions such as von Hippel Lindau disease have a very high risk of kidney cancer,

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[9] Relationships that are based on small numbers may reflect random chance, and there are hazards of drawing inferences from a small dataset. One of the problems that can arise from relying on small numbers is illustrated by the following example: A fair coin that is flipped a thousand times will produce results strikingly close to 50% heads and 50% tails, whereas flipping the coin just six times can result in 100% heads—a statistically unstable, random clustering pattern that it would be error to apply on a larger scale.

and there is some argument for screening in this limited subset of people (unrelated to PFAS exposure).

The epidemiologic literature shows inconsistent and weak associations between one type of PFAS—PFOA—and kidney cancer. In some studies there are trends between highly elevated blood levels of PFOA and diagnosis of kidney cancer, but no association is seen in other cohorts, worker studies, and community studies. Overall, the data associating kidney cancer with PFOA exposure are weak and lack consistency across studies. (Barry 2013; Steenland 2012; Vieira 2013; Raleigh 2014; Shearer 2020)

The natural course of renal cell carcinoma is such that without screening, 65% of persons with the disease are diagnosed when the cancer is contained to the kidney, and 93% of patients are alive at 5 years. (American Society of Clinical Oncology 2019) The potential benefit from screening would be a potential small improvement in health outcome, though with an even smaller increase in survival. Any possible benefit is more than offset by the harms associated with screening which is why screening for kidney cancer is not recommended. The harms are substantive and stem largely from the large number of false positive test results from scans, which would lead to further diagnostic testing and more invasive procedures, false positive results and complications, and overdiagnosis and overtreatment.

Screening for renal cancers, if there were a sound rationale, might begin with a urinalysis. This test looks for microscopic red blood cells in the urine but, in addition to kidney cancer, blood in the urine (hematuria) may be caused by urinary tract infections, menses or other causes of vaginal bleeding, bladder cancer, kidney stones, interstitial kidney disease, and other disease processes. Thus, a urinalysis has low specificity and limited value in screening. Evaluation for hematuria after urinalysis usually includes additional blood tests and an ultrasound, which are often followed by CT and MRI scans. The scans often cannot distinguish between benign or malignant tumors. Even tumors classified as malignant often remain indolent. (Chandrasekar 2018) Invasive procedures and surgery are frequently required for diagnosis. Positive findings unrelated to cancer on the scans and in blood tests often result in additional cascades of testing to evaluate these findings. A number of errors are common in interpreting CT scans of renal masses. (Krishna 2017) False diagnosis and overdiagnosis rates are very high. This means that many people will be subjected to treatments, including surgery, that may cause harm but will not benefit them.

Exhibit C ("Algorithm - Hematuria Screening for Kidney Disease and Kidney Cancer") shows the initial steps in investigating an abnormal result in a urinalysis. There are multiple analyses performed within a urinalysis test, and thus the likelihood of a false positive result is higher than if a single analysis is performed. The algorithm in Exhibit C looks at hematuria, which is one finding that can be seen early on with kidney disease or kidney cancer. Other components of the urinalysis such as protein, white blood cells and casts could each lead to a stepwise progression in further testing and evaluation. The urinalysis and additional testing—including ultrasound and abdominopelvic CT—often result in false positives. The patient then may undergo CT with contrast and cystoscopy which can have serious adverse effects. An evaluation that started with a urine sample to check for kidney disease in a healthy person leads to many additional tests and procedures and may not conclude with any certainty (no definitive cause found), or may find a tumor of indeterminate nature. Surgery may be required to determine with greater certainty the

nature of the tumor. There may be challenging discussions and decisions, with the end result being one or more findings, such as a slowly progressive kidney disease, a benign tumor in the adrenal glands, a renal or bladder cancer that is or is not treatable and that does or does not respond to treatment, enlarged pelvic lymph nodes, or possible cyst in the left ovary, all of which leave uncertainty and anxiety about further evaluation and future health.

Looking for renal cell carcinoma with a CT or MRI also raises a very challenging and common problem: incidental findings, in this case somewhere in the abdomen or pelvis or soft tissue or bones, that are unrelated to the kidney. The incidental findings may be a density, mass, collection of lymph nodes, thickening or other ill-defined visual reading that, once investigated, may reflect normal structures, or may reveal abnormalities, ones that are clinical variants and do not contribute to disease, or false positives, or pathologic findings with a range of known or unknown potential impacts. These findings often trigger invasive follow-up testing (with all the attendant risks) in order to address concern about the possibility of an unknown condition. (American Cancer Society 2020b; Mazziotti 2017) High levels of anxiety are often seen with the additional and unexpected testing, as well as a fear of cancer.

In summary, the natural histories of the diseases grouped as renal cancer vary, the incidence of renal cancer is low in the general population, and the literature does not support a causal relationship between renal cancer and PFOA exposure. In terms of screening, the tests are not specific, false positive and incidental findings are relatively common, and often one or more invasive procedures may be performed if a mass is found. Screening for renal cancer is not recommended, even for those with elevated risk attributable to factors such as tobacco and obesity. (American Cancer Society 2020b) Screening for kidney cancer in the proposed class to find renal disease related to PFAS exposure would cause harm to individuals with virtually no chance of reducing mortality from early detection of kidney cancer attributable to PFAS exposure.

2. Testicular Cancer

The incidence of testicular cancer is estimated to be between 2 and 5 per 100,000 males, representing only 1-2% of all male cancers. The cancer occurs predominantly in younger men, ages 15-34.

Testicular cancer found on screening does not have an improved course or prognosis compared with treatment after symptoms (such as testicular swelling or discomfort) develop. The USPSTF has concluded that there is adequate evidence that the benefits of screening for testicular cancer are small to none, given the low incidence of the condition and the favorable outcomes of treatment once symptoms manifest. All stages of the disease are curable, and no advantage (that outweighs harms of screening) to finding the early cancer has been seen. There is little evidence supporting routine testicular cancer screening. For these reasons, the USPSTF recommends against screening for testicular cancer in adolescent or adult males. (USPSTF 2016)

Examination for testicular cancer, if performed, can be done as part of a physical exam with a healthcare provider or by self-exam. There currently exists no standard or routine screening test for detection of testicular cancer. If a lump is found in the testicle by the patient or as part of a physical exam, further testing (blood testing, scrotal ultrasound, or CT of the chest, abdomen,

and pelvis) may be done to determine if the lump is cancerous. This is done in primary care practices everywhere.

Despite the fact that screening for testicular cancer is generally not recommended and can be performed where indicated during regular primary care, there is no benefit to a proposed class-wide monitoring program. Older men would undergo questions and examination for a disease that virtually never occurs in their age group. Thus, for these men there is nothing gained by testing, yet they would be subjected to the associated discomfort and harms. In older men, such investigations would find many false positives such as hydrocoele, orchitis, hernias, epididymitis, etc. These are conditions that may result in further testing as a result of being discovered, with attendant anxiety, discomfort and risk of harm from diagnostic procedures. (NCI, Testicular Cancer Screening PDQ)

3. <u>Liver Function Abnormalities and Liver Disease</u>

Liver function tests (LFTs) refer to blood tests that measure a group of enzymes in the blood that are generally seen as reflecting a possible liver disease when the measured levels are beyond population norms. Analysis of this set of biomarkers is complex, in that abnormally high levels may indicate liver, heart, lung, gall bladder or lung disease; substance abuse; medication use; or immunologic or endocrine processes, among other things, and the test levels tend to increase with age.

The LFTs may reflect acute or chronic conditions that may be already known to the individual, or the results may reflect a range of normal for that person. Some examples of the range of conditions that may show elevated liver enzymes are hepatitis, alcoholic liver disease, gallstones, pancreatitis, acute alcohol binge, metastatic cancer in the liver, hepatoma and cirrhosis. USPSTF recommends screening for hepatitis C—a disease with effective treatment and a screening test with high accuracy—as a means to reduce the incidence of serious adverse outcomes, including liver cancer. USPSTF does not recommend screening with LFTs for any other disease.

There is significant risk involved in checking LFTs in asymptomatic persons. The risk of adverse health events is high given the almost certain probability of finding an abnormal liver function test, such as GGT, among the multiple liver function tests in the testing panel and among many persons tested. Often such individual findings, even outside typical ranges, are not indicators of a clinically significant disease or condition. This leaves open a wide range of tests to pursue a diagnosis where many conditions and behaviors may play a role, with the probability of invasive procedures such as liver biopsy. In addition, liver scans increase the risk of detection of incidental liver lesions that would generally require further evaluation and sometimes require invasive testing, which would lead to even more false positive results, anxiety, and complications from further investigations. (Fergusson 2012) Liver function tests have low specificity and low sensitivity for diagnosing most conditions.

Thus, liver function testing can and often does result in a cascade of further testing with procedures that cause complications and anxiety. **Exhibit E** (“Liver Disease/Liver Cancer”) shows an example of an algorithm for screening with LFTs and the types of follow-up scans that are done after finding a result that is “abnormal”—which often just means slightly elevated. The chance of finding liver disease caused by PFAS is vanishingly small since there is no evidence

that PFAS causes a specific liver disease and since the tests are so broad and nonspecific. (C8 Science Panel 2012) For example, non-alcoholic fatty liver disease is a common disease associated with obesity and for which the treatment is lifestyle modification. The diagnosis of the various forms of liver disease is best done by the person's primary physician, who would also focus on nutrition and exercise counseling. Weight loss is the most important intervention for preventing and reducing the impact of this disease.

LFT abnormalities are common and due to many causes, some reflecting transient inflammation (such as recent alcohol ingestion) and some more chronic (such as cirrhosis or viral hepatitis) and possibly requiring treatment. Viral hepatitis prevention is addressed with the primary care physician, generally through vaccines for everyone and hepatitis C testing (and treatment) where specifically indicated.

The number of false positive results and the extensive cascade of testing would be magnified were the LFT screening repeated on a periodic basis, such as annually. The anxiety and emotional and physical impact can be particularly pronounced for the elderly. For the general community, counseling to prevent excessive alcohol intake and counseling to prevent and reduce obesity are recommended instead in order to reduce the risk of liver disease. (USPSTF 2018a; USPSFT 2018b) Routine LFT testing is unnecessary and often results in adverse health outcomes in persons who were healthy before undergoing screening.

Conclusion

In summary, the plaintiff's proposal for a class-wide medical monitoring program fails to comport with well-established scientific and medical criteria for screening. In fact, ATSDR's guidance is directly the opposite of what the plaintiff is proposing. Among the many flaws in plaintiff's analysis are the following:

1. Plaintiff fails to address the many existing individual factors that necessarily provide the backbone for the design and success of an effective medical monitoring program

- Plaintiff ignores the many important individualized differences among class members that should be addressed *both* in the initial decisions of whether to screen and what to screen particular individuals for, as well as in the follow up decision-making regarding how to respond to the results of that initial screening. As discussed above, the plaintiff himself exemplifies the variation in current and past medical conditions, regularly recurring screening already being received, risk factors for disease and risk factors for adverse effects from the screening cascade, as well as his personal preferences regarding screening. A medical monitoring program designed without clear deference to these factors is not relevant or beneficial for the persons to be screened.

2. Plaintiff fails to identify any basis for asserting that proposed class members are at a significantly increased risk based on exposure to PFAS.

- The plaintiff fails to consider the important differences in the proposed class members' potential exposures and in their individual backgrounds—considerations that directly impact the assessment of whether they are at an increased risk of a particular disease and

whether monitoring for that disease is warranted and could be beneficial to an extent that outweighs the potential complications and adverse effects of testing.

- Plaintiff uses an arbitrary cutoff (0.05 ppt of PFOA and 0.05 ppt of some other form of PFAS in blood serum) to define the class that he assumes is at increased risk of disease from PFAS exposure and should be offered his medical monitoring. The level of 0.05 ppt is approximately four orders of magnitude (10^4) below the geometric mean blood level in the US general population; using this blood level as a cutoff for medical monitoring would thus include almost the entire US population—more than 300 million people. However, the plaintiff offers no justification for using this level, and does not identify any scientific evidence that 0.05 ppt represents a threshold above which persons are at any risk of any disease—much less at a significantly increased risk of disease. Because the class, as defined, essentially encompasses the general population, by definition it is not at significantly increased risk compared to the general population and is therefore an inappropriate target population for medical monitoring. To the extent that plaintiff seeks a monitoring program as a means of studying the health effects, if any, of PFAS exposure, that is not a proper form of medical monitoring either.

- It is not scientifically sound to assume that, if a chemical is detected in a person, that means that toxic effects are possible or likely to occur. Plaintiff appears to be assuming that any exposure, no matter how small, is harmful—a concept which has been rejected by modern medicine. Though PFAS is found in the blood of virtually every person, this does not mean that the chemical increases the risk of adverse health effects in everyone. ATSDR has found that there are no biomarkers of health effects for PFAS, and blood levels only confirm exposure (which is virtually universal). (ATSDR 2019) Further, ATSDR has clearly stated that causation has not been established between PFAS exposure and any adverse health effects at any dose in humans. (ATSDR 2018; ATSDR 2019) In fact, ATSDR advises clinicians that "[t]here is no established PFAS blood level at which a health risk is expected, nor is there a level that is clearly associated with past, current, or future health problems." (ATSDR 2019) Moreover, federal and state regulatory exposure limits (such as those set or suggested by EPA and other organizations), are based on very conservative assumptions, including about the amount of water ingested, and with safety and uncertainty factors added. These exposure limits are designated as part of policies to protect even susceptible populations from health effects and are not intended to inform clinical decision-making. And still, drinking water with PFAS levels set by any of the regulatory agencies that have established such levels would result in blood levels far in excess of the threshold that the plaintiff proposes to define the medical monitoring class in this case.

<u>3. Plaintiff fails to define the medical monitoring he is proposing</u>

- The plaintiff fails to meet the fundamental requirement that medical monitoring considerations be premised on the assessment of specific medical tests for the detection of specific medical conditions for individuals at a significantly increased risk of those conditions. The plaintiff does not present a plan for testing or evaluation of the associated harms and benefits. Plaintiff fails to take into account the harms that are likely to result when screening decisions do not consider the individual. In order to understand and

communicate the potential benefit of screening for particular diseases to patients and physicians, the proposed plan must lay out the full cascade of testing, with risks at each decision point. That involves, for example, stating the risks of false positive and false negative results at each step, the next testing options, the tests' accuracy, and the risk of adverse physical or mental harm along the way.

- Since the full cascade of testing and associated risks is not laid out, the risks and benefits cannot be understood and compared, and therefore fully informed shared decision-making with the individual being screened is not possible. An individual offered screening in a program without this information would be facing a series of tests and procedures and interventions, potentially with the prospect of no health benefits while also experiencing a range of adverse impacts to mental and physical health. A monitoring program cannot be accepted or even assessed for appropriateness and effectiveness until there is a plan for the screening tests, the subsequent testing, and the procedures required for diagnosis.

- The plaintiff does not provide any information about the sensitivity, specificity, or positive predictive value of the tests he would include in a monitoring program, or the prevalence of the diseases he would monitor for, nor does he address the vulnerability of any individuals to the proposed testing and the cascade of procedures likely to follow.

4. Plaintiff cannot design an efficacious medical monitoring program based on class-wide generalities

- The propriety of a proposed medical monitoring program turns on the relative benefits and risks that the proposed program offers to its recipients. The benefits of any monitoring program depend directly on the level of risk imparted by the exposure at issue, which in turn depends directly on the magnitude of the exposure and how that exposure relates to the available epidemiological evidence on dose-threshold and dose-response (which also varies for each individual health endpoint being assessed). Because exposure level is inherently and predominately an individualized issue, as demonstrated by the widely varying exposure levels documented in the proposed class, it is scientifically inappropriate to assess monitoring on a class-wide basis here. Similarly, the risks of performing monitoring tests turn heavily on individualized issues, such as background medical history, and therefore also cannot be assessed on a class-wide basis. In real world screening, persons without symptoms are individually checked for whether they are at an increased risk of a particular disease, whether they already undergo the potential testing, whether the disease was diagnosed in the past, whether the organ was operated on in the past or removed, etc. After review of these and other personal health factors, then a clinician discusses the harms and benefits of screening with the potential participant. As a result of inter-individual differences, tests that benefit one person with a very high exposure and high risk of a specific disease for which screening is beneficial would be more likely to cause health problems for another person with different exposure related disease risks, age, health status and other personal factors. Thus, neither the benefits nor the risks of screening are susceptible to class-wide assessment. One cannot reliably create a medical monitoring plan that includes specific persons before these individualized factors are known.

- The plaintiff improperly blurs and overlooks these important principles. Instead, he advocates for ill-defined and broad-based monitoring for unspecified conditions in an inappropriately broad population of individuals, without any consideration of the many important individual factors of relevance, in direct contradiction to the well-accepted criteria for medical monitoring from ATSDR and others, and in direct contradiction to the well-reasoned recommendations from ATSDR on this very subject.

Supplementation

I reserve the right to supplement this report based on any new or additional data, and to respond to the testimony of others. In addition, I reserve the right to use graphics or other exhibits to further address the matters discussed in this report.

Declaration

Subject to the above regarding supplementation, this report contains a complete statement of all opinions I will express in relation to plaintiffs' motion for class certification in this matter and the basis and reasons for them, as well as the facts or data I considered in forming these opinions. I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge.

Jessica Herzstein, M.D., M.P.H
Dated: December 14, 2020

Exhibit A

Curriculum Vitae

JESSICA HERZSTEIN, M.D., M.P.H.

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EDUCATION:

Yale University School of Medicine
New Haven, Connecticut
M.P.H. in Environmental Health, 1989

Yale University School of Medicine
New Haven, Connecticut
M.D., 1983

Harvard College, Cambridge, Massachusetts
A.B. Cum Laude in Chemistry, 1978

University of California at Berkeley, 1974–1976

MEDICAL TRAINING:

Fellowship: Yale University School of Medicine, Department of Medicine
Dana Fellow in Occupational and Environmental Health, 1987–1989

Research on cellular mechanisms of toxin-induced lung disease

Residency: Beth Israel Hospital and Harvard University School of Medicine
Internal Medicine and Primary Care, 1985–1987

Internship: University of California at San Francisco
Internal Medicine, 1983–1984

PROFESSIONAL EXPERIENCE:

1995-present Consultant and President, Environmental Health Resources, P.C.

Advising organizations in the nonprofit, public and private sectors on clinical, public health, risk management and safety issues including covid pandemic response and communications, health crisis planning and preparedness, hazardous exposures, international travel, and periodic preventive health services.

2012 – 2016 Member, United States Preventive Services Task Force (5 year term)
Appointed by HHS to a panel of 16 primary care clinicians who develop evidence based recommendations that form the basis for preventive health services in the U.S.

1997–2014	Global Medical Director, Air Products and Chemicals, Inc. Responsible for health programs for 25,000 workers in over 40 countries including pandemic planning and management, industrial hygiene and risk assessment, chemical safety in manufacturing and transport, health surveillance, international travel health, fitness for work and accommodation, health crisis preparedness and crisis management, mental health and wellbeing. Provided clinical services to employees at headquarters in Pennsylvania.
2015 --	Professorial Lecturer, Department of Occupational and Environmental Health, The Milken Institute School of Public Health, George Washington University
2006 –	Lecturer, University of Pennsylvania School of Medicine Department of Occupational and Environmental Health
1996–2004	Visiting Lecturer in Occupational Medicine Department of Environmental Health Harvard School of Public Health
1995–1997	Medical Director Defense Contract Management District East Department of Defense Responsible for medical surveillance for DOD employees in contractor settings; also clinical assessment and intervention for DOD employees in Boston
1996–1998	Consultant to Harvard Institute of International Development and U.S. Agency for International Development (Eastern Europe)
1996–1997	Associate Clinical Professor of Medicine Temple University School of Medicine
1992–1995	Assistant Clinical Professor of Medicine Temple University School of Medicine
1992–2000	Clinical Faculty, Department of Medicine, Abington Memorial Hospital, Abington, Pennsylvania
1992–1995	Director, Center for Occupational & Environmental Health Abington Memorial Hospital Started and directed a clinical center for occupational health for Philadelphia area industrial and office employees; responsible for patient care and resident teaching in the internal medicine residency program, in inpatient and outpatient settings
1990–1992	Assistant Professor of Medicine, Department of Medicine and Department of Community and Preventive Medicine Division of Occupational and Environmental Health Medical College of Pennsylvania Responsible for Inpatient and outpatient care, teaching residents and students, and research on occupational asthma
1987–1989	Occupational Medicine Physician, Employee Health Services Yale–New Haven Hospital, New Haven, CT

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ACADEMIC POSITIONS AND GRANTS:

2016 --	Professorial Lecturer, Department of Occupational and Environmental Health, The Milken Institute School of Public Health, George Washington University
2007 –	Visiting Lecturer in Occupational and Environmental Health, University of Pennsylvania School of Medicine
1996–2004	Visiting Lecturer in Occupational Medicine Department of Environmental Health Harvard School of Public Health
1997–2004	Visiting Lecturer, Northwestern University School of Medicine, Preventive Medicine Department
1996–1997	Associate Clinical Professor of Medicine, Department of Medicine Temple University School of Medicine
1992–1995	Assistant Clinical Professor of Medicine, Department of Medicine Temple University School of Medicine
1990–1992	Assistant Professor of Medicine, Department of Medicine and Department of Community and Preventive Medicine Medical College of Pennsylvania

BOARD CERTIFICATION:

1987	American Board of Internal Medicine
1990	American Board of Preventive Medicine, Specialty of Occupational Medicine

OTHER CERTIFICATION:

Certified Medical Review Officer (MROCC)

MEDICAL LICENSURE:

District of Columbia (active)
Past state medical licenses: California, Massachusetts and Pennsylvania

PROFESSIONAL ORGANIZATIONS:

Fellow, American College of Physicians
Member, Council on Foreign Relations
Fellow, American College of Occupational and Environmental Medicine

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BOARDS / ADVISORY BOARDS:

Partners Global (previously Partners for Democratic Change), Board of Trustees (2015 to present)

Forum on Public- Private Partnerships for Global Health and Safety
Institute of Medicine
National Academy of Science (2013 to present)

Advisory Committee for ASPEN-IMCO Health Initiative, IMCO (Instituto Mexicano de la Competitividad) (2014 to 2016)

Advisory Board, Global Business Group on Health at the
National Business Group on Health (2010-2014)

Advisory Board, Global Health and Development
The Aspen Institute (2010 to 2016)

National Institute for Occupational Safety and Health (NIOSH)
National Occupational Research Agenda (NORA) Liaison Committee (2010 to 2014)

Advisory Committee for PCORI Grant, Improving Health Outcomes with Back Pain
(2013 – 2015)

PEER REVIEW ACTIVITIES:

Peer Reviewer: Occupational Medicine
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Exhibit B

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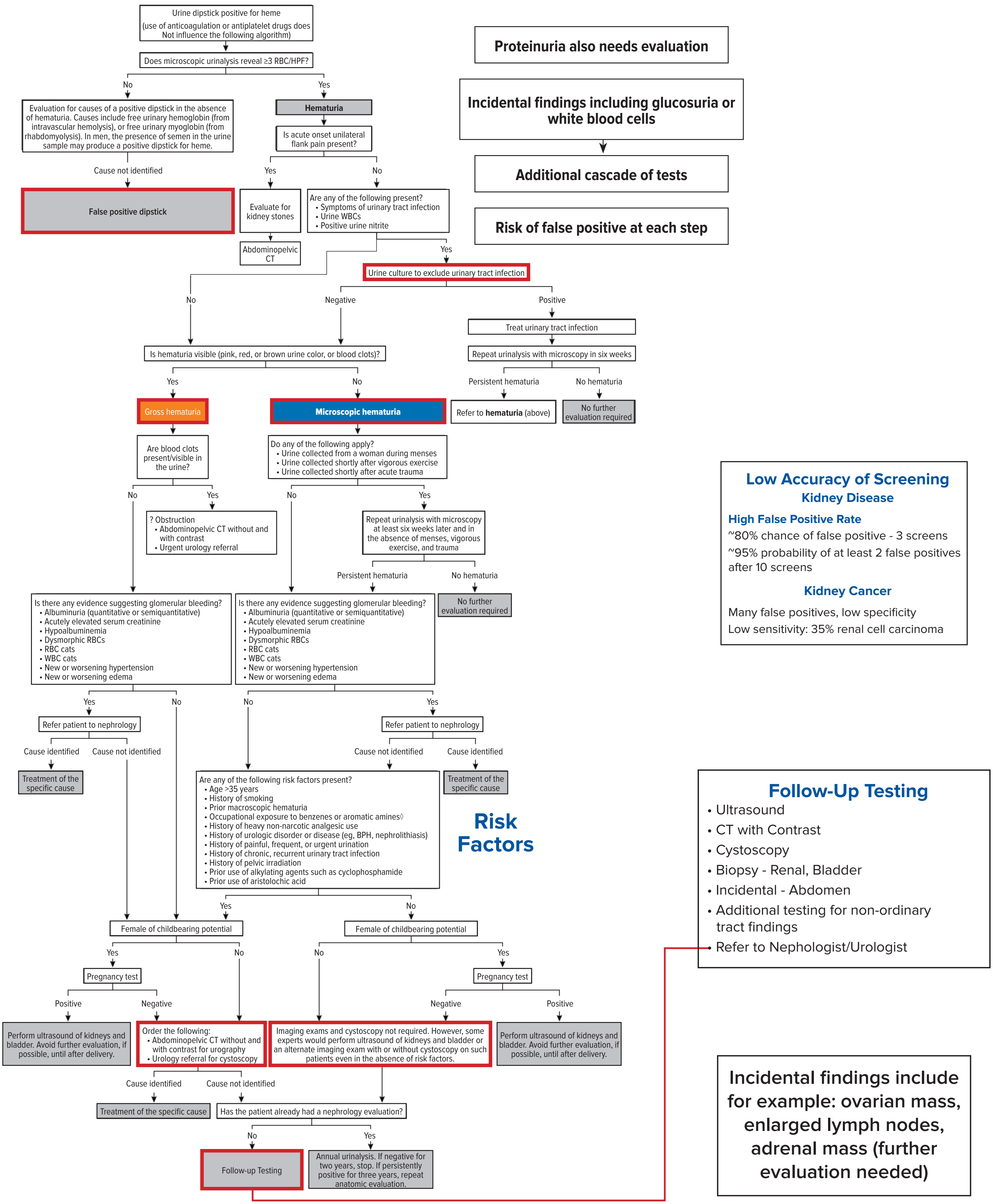
Exhibit C

Algorithm - Hematuria Screening for Kidney Disease and Kidney Cancer*



RBC: red blood cell; HPF: high-power field; WBC: white blood cell; CT: computed tomography; BPH: benign prostatic hyperplasia.

*Adapted from UpToDate Inc., Walters Kluwer 2020.

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Exhibit D

What Is Required for Medical Monitoring?

Population Epidemiology

CAUSATION

Toxin and Human Disease Connected?

Studies of highly exposed workers, communities, or other exposed persons

"Association" if study shows general relationship between exposure and disease

Causative of specific human disease?

Evaluate scientific studies based on accepted criteria, such as:

- Strength
- Dose Response Relationship
- Temporality
- Consistency
- Biological Plausibility
- Coherence

Yes

No

Prevalence of the Disease

Correlating with dose

No

Yes

No Medical Monitoring

Periodic Screening per USPSTF*, such as:

Blood Pressure
Weight
Cholesterol
Screening for:
- Hepatitis B & C
- Diabetes
- Cervical Cancer
- Colon Cancer
- Breast Cancer

*Testing depends on age, sex, family history, ethnic origin, lifestyle factors, and other.

Individuals

Consider Medical Monitoring

Is There Risk of a Specific Disease Due to Exposure?

Is Exposure Level (Dose) Sufficient?

Source
Concentration
Amount / Frequency
Duration

Is Risk of Disease Significantly Elevated?

No

Benefits/Harms Analysis
(Including Individual Considerations)

Test Accuracy
- Sensitivity
- Specificity
- Prevalence

Positive Predictive Value
Impact of Serial Testing (Includ. False Pos.)
Cascade of Testing
Invasive Procedures
Incidental Findings
- Additional Evaluations, Complications

Labeling
Anxiety/Uncertainty
- Lack of Closure

Age, Predicted Lifespan, Comorbidities
Effective Treatment for Condition
Improved Outcome for Age, Stage of Disease, and Comorbidities
Extended Lifespan

No

Do Benefits Outweigh Harms?

Shared Decision Making

Discussion With Caregiver
Personal Preferences of Individual:
- Testing
- Follow Up Evaluation
- Diagnostic Procedures
- Treatment
- Psychological Impact

Yes

Individualized Medical Monitoring

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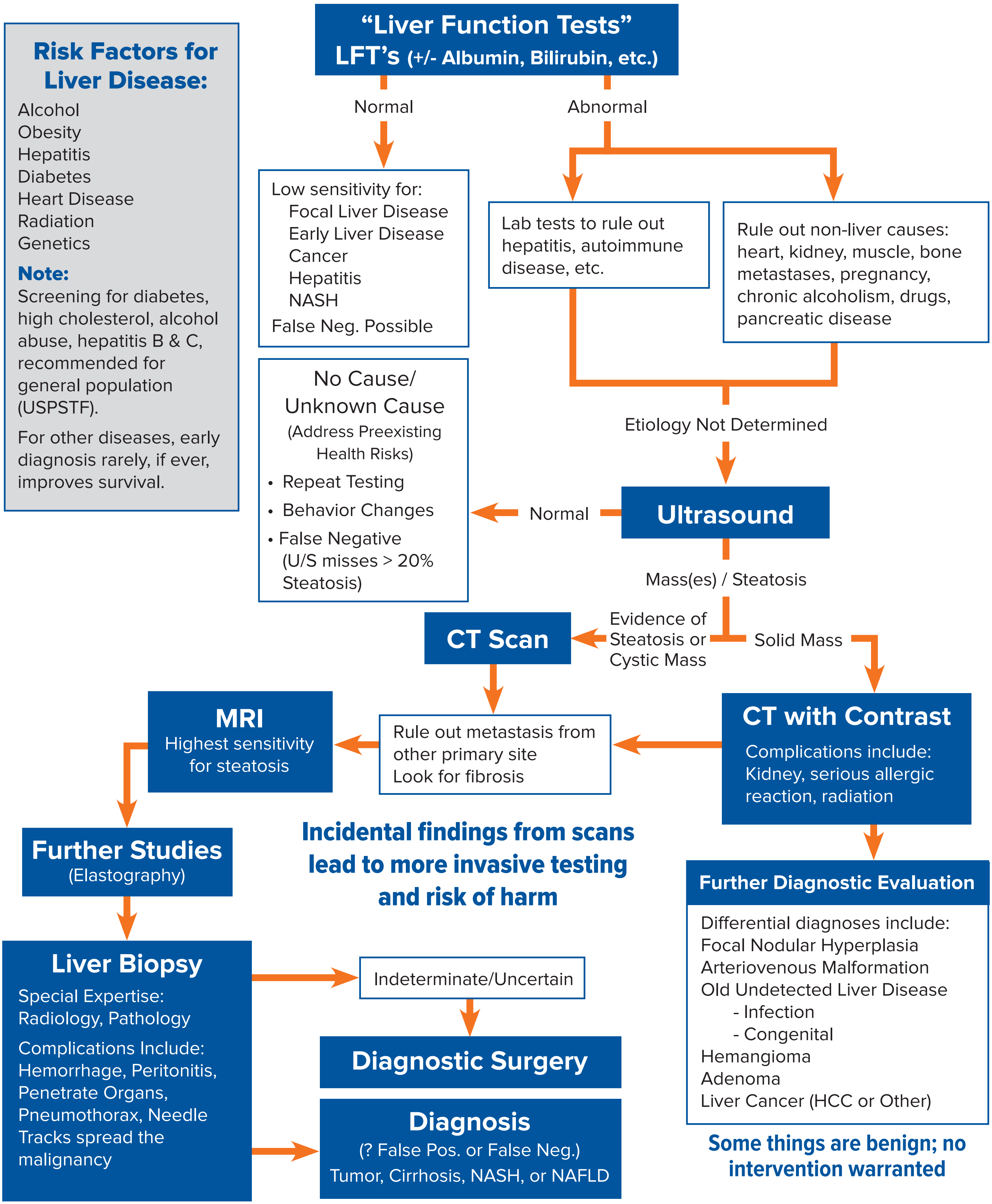
Exhibit E

Liver Disease / Liver Cancer



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